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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary

Application No.

10/823,866

Applicant(s)

STERN ET AL.

Examiner

UNSU JUNG

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 November 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-14, 16, 20, 25-33 and 53-55 is/are pending in the application.
- 4a) Of the above claim(s) 10, 14, 26-33 and 53-55 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 11-13, 16, 20 and 25 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 April 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-940)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on November 12, 2009 has been entered. The submission included Declaration of Lawrence J. Stern, Ph.D. under 37 CFR 1.132 and cancellation of claims 35, 36, 38-50, 52, 56, and 57.

Status of Claims

2. Claims 1-14, 16, 20, 25-33, and 53-55 are pending, claims 10, 14, 26-33, and 53-55 have been withdrawn from consideration, and claims 1-9, 11-13, 16, 20, and 25 are currently under consideration for patentability under 37 CFR 1.104.

Priority

3. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The instant application, filed on April 14, 2004, claims priority to U.S. Provisional Patent Application Serial No. 60/463,379, filed on April 16, 2003.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-7, 11, 12, 16, 20, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (WO 97/46256, Dec. 11, 1997) in view of Rhode et al. (U.S. Patent No. 6,232,445, May 15, 2001), Lehmann et al. (U.S. Patent No. 5,939,281, Aug. 17, 1999), Yurino et al. (U.S. Patent No. 6,127,125, Oct. 3, 2000), and Alfenito (U.S. Patent No. 6,355,419 B1, Mar. 12, 2002).

Webb et al. teaches an array (see entire document) comprising a substrate (support, p49, lines 7-18) and a plurality of MHC molecules complexed with antigen-derived peptides (p18, lines 9-17 and p50, line 1-p51, line 25) immobilized in spatially distinct areas on the substrate (wells of microtiter plates, p80, lines 24-31). Webb et al. further teaches that activation of T-cells is characterized by proliferation of the responsive T cell population coordinated with the selective production of cytokines (p16, lines 28-32). With respect to claim 20, Webb et al. teaches that the different cytokine profiles such as IL-2, IL-4, IL-5, IL-10, and IFN- γ characterize functional phenotypes of type 1 and type 2 T-cells (p16, lines 8-23).

With respect to claims 11 and 12, Webb et al. teaches an array, further comprising costimulatory molecules immobilized in the spatially-distinct areas on the substrate (p49, lines 7-14), wherein the costimulatory molecules are costimulatory antibodies (p21, line 27-p22, line 6).

With respect to claim 16, Webb et al. teaches an array, wherein the MHC molecules comprise class II MHC molecules (p18, lines 20-30).

However, Webb et al. is silent on disclosing that the each group of spatially distinct areas comprises a plurality of different MHC-peptide complexes and that the array, further comprises anti-factor antibodies specific for secreted factors, immobilized spatially-distinct areas on the substrate. Webb et al. further fails to teach that the substrate is flat. Finally, Webb et al. fails to teach that at least one hydrophobic barrier surrounds a plurality of the spatially-distinct areas and each of the spatially-distinct areas is not surrounded individually by a separate hydrophobic barrier, such that when a single volume of sample is applied inside of the at least one hydrophobic barrier, all areas in the plurality of said spatially-distinct areas are in contact with the single volume of sample.

With respect to claims 1 and 2, Rhode et al. teaches that MHC complexes can be used to screen immune cells such as T-cells expressing a desired target structure in vitro (see entire document, particularly column 4, lines 24-26). A wide variety of peptides can be presented for interaction with T-cells (i.e. a library of different peptides can be linked to a MHC molecule for presentation of T-cells, column 5, lines 11-17). With respect to claim 5, Rhode et al. further teaches that an array of MHC complexes can be formed on a substrate such as 96-well plates (column 55, lines 45-51) and MHC molecules are selected from Class I MHC molecules, Class II MHC molecules, or Class I and Class II MHC molecules (column 3, lines 36-45).

With respect to claims 1 and 25, Lehmann et al. teaches a method of detecting secreted cytokines by activated T-cells using cytokine capture assay (see entire document, particularly, column 3, lines 14-36). The cytokine capture assay of Lehmann

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et al. involves plating both the activating molecules (test antigen peptide) co-incubated with immobilized cytokine capture antibodies (column 3, lines 14-36).

With respect to claim 1, Yurino et al. teaches a biochip comprising a plurality of regions bound with various probes (see entire document, particularly Abstract). The biochip has a flat upper surface of a generally equal height. As a result, a sample can be applied to the entire features of the biochip (column 6, lines 48-60).

With respect to claims 6 and 7, Yurino et al. teaches a substrate comprising glass (column 6, lines 48-60), which is optically transparent.

Alfenito teaches an array of probes comprising a nylon membrane; a plurality of subarrays of probes on the nylon membrane, the subarrays comprising a plurality of individual spots wherein each spot is comprised of a plurality of probes of the same sequence; and a plurality of hydrophobic barriers located between the subarrays on the nylon membrane, whereby the plurality of hydrophobic barriers prevents cross contamination between adjacent subarrays (see entire document, particularly column 3, lines 5-14). Many samples may be interrogated as pools at the same subarrays or independently with different subarrays within one support (column 35, lines 55-63).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ plurality of different MHC-peptide complexes of Rhode et al., which are formed by a MHC molecule complexed with a library of different peptides, in the array of Webb et al. in order to screen T cells expressing a desired target structure in vitro. The advantage of screening T cells for their interaction with a plurality

of different peptides complexed to a MHC molecule provides the motivation to combine teachings of Webb et al. and Rhode et al. with a reasonable expectation of success.

In addition, it would have been obvious to one of ordinary skill in the art at the time of the invention to include anti-factor antibodies specific for secreted factors co-immobilized on the spatially-distinct areas of the substrate with activating molecules as taught by Lehmann et al. in the array of Webb et al. in order to perform cytokine capture assay for detecting secreted cytokines by the activated T-cells. The advantage of allowing T-cell activation and capturing of the secreted cytokines following the activation in the same area of the substrate provides the motivation to combine teachings of Webb et al. and Lehmann et al. with a reasonable expectation of success as the use of co-immobilized MHC molecules complexed with antigen-derived peptides and anti-factor antibodies specific for secreted factors would eliminate additional steps of supernatant harvesting and transferring of the supernatant to another substrate for cytokine detection assay necessary to determine cytokine profile of the activated T-cell populations.

Further, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ the flat surface for the protein microarrays of Webb et al. in view of Rhode et al. and Lehmann et al. as taught by Yurino et al. in order to apply a sample to all the features of the protein microarray. The ease of applying sample to desired regions of the protein microarray provides the motivation to combine teachings of Webb et al. in view of Rhode et al. and Lehmann et al. and Yurino et al. with a reasonable expectation of success. In addition, because both flat and non-flat

substrates be used to provide support for the protein arrays, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the multi-well plate format of Webb et al. in view of Rhode et al. and Lehmann et al. for the flat substrate format of Yurino et al. to achieve to predictable result of providing a suitable support for the protein array.

Finally, it would have been obvious to one of ordinary skill in the art at the time of the invention to provide at least one hydrophobic barrier surrounding a plurality of the spatially-distinct areas (each of the spatially-distinct areas is not surrounded individually by a separate hydrophobic barrier) such that when a single volume of sample is applied inside of the at least one hydrophobic barrier, all areas in the plurality of said spatially-distinct areas are in contact with the single volume of sample as taught by Alfenito in the array of Webb et al. in view of Rhode et al., Lehmann et al., and Yurino et al. in order to prevent cross contamination between adjacent subarrays for simultaneous analysis of multiple samples. The advantage of analyzing multiple samples simultaneously with cross contamination provides the motivation to combine teachings of Webb et al. in view of Rhode et al., Lehmann et al., and Yurino et al. and Alfenito with a reasonable expectation of success.

With respect to claim 1 and all dependent claims thereof, the recitation that spatially-distinct areas are configured to allow contact with one sample at essentially the same time and with the same sample is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. *In re Hutchison*, 69 USPQ 138 (CCPA 1946); *In re Swinehart*, 169 USPQ 226 (CCPA 1971);

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and *In re Schreiber*, 44 USPQ2d 1429 (Fed. Cir. 1997). A patent applicant is free to recite features of an apparatus either structurally or functionally. See *In re Swinehart*, 439 F.2d 210, 212, 169 USPQ 226, 228 (CCPA 1971) (" [T]here is nothing intrinsically wrong with [defining something by what it does rather than what it is] in drafting patent claims."). Yet, choosing to define an element functionally, i.e., by what it does, carries with it a risk. As our predecessor court stated in *In re Swinehart*, 439 F.2d at 213, 169 USPQ at 228:

where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on

Therefore, the feature of "the spatially-distinct areas are configured to allow contact with one sample at essentially the same time and with the same sample" would be an inherent characteristic of the array of Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito since the array of Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito meets all the structural limitations of the claimed array.

With respect to claims 3 and 4, Yurino et al. teaches that an entire array can be used to assay a plurality of different analytes in a single sample as set forth above. Given the teachings of Yurino et al., it would have been obvious to one of ordinary skill in the art at the time of the invention to provide a hydrophobic barrier surrounding all of the spatially distinct areas on the array substrate in order to simultaneously analyze analytes that may be present in a single sample binding to probes on all the spatially

distinct areas of the array. The advantage of assaying parallel for plurality of different analytes in a sample provides the motivation to provide a hydrophobic barrier surrounding all of the spatially distinct areas on the array substrate with a reasonable expectation of success. Further, Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito discloses the claimed invention except for a single hydrophobic barrier surrounding all of the spatially distinct areas. It would have been obvious to one of ordinary skill in the art at the time of the invention to arrange a hydrophobic barrier surrounding all of the spatially distinct areas, since it has been held that rearranging parts of an invention involves only routine skill in the art. *In re Japikse*, 181 F.2d 1019, 86 USPQ 70 (CCPA 1950).

8. Claims 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (WO 97/46256, Dec. 11, 1997) in view of Rhode et al. (U.S. Patent No. 6,232,445, May 15, 2001), Lehmann et al. (U.S. Patent No. 5,939,281, Aug. 17, 1999), Yurino et al. (U.S. Patent No. 6,127,125, Oct. 3, 2000), and Alfrenito (U.S. Patent No. 6,355,419 B1, Mar. 12, 2002) as applied to claim 1 above, and further in view of Tom-Moy et al. (U.S. Patent No. 6,235,488, May 22, 2001).

Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito teaches an array comprising a substrate and an array of MHC molecules complexed with antigen-derived peptides and costimulatory antibodies immobilized in spatially distinct areas on the substrate as set forth above. Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito further teaches that biotinylated MHC

molecules can be immobilized on the avidin-coated substrate via biotin-avidin linked interactions with the substrate (p81, lines 10-16). However, Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito fails to teach that streptavidin can be used in place of avidin.

With respect to claims 8 and 9, Tom-Moy et al. teaches that streptavidin can be a substitute for avidin since it has similar biotin-binding properties (see entire document, particularly column 4, lines 62-63).

Therefore, Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito meets the limitations of claims 8 and 9 except that it employs avidin rather than streptavidin to coat the substrate surface for immobilization of biotinylated MHC molecules. However, because these two elements were art-recognized equivalents at the time of the invention in the specific binding applications as taught by Tom-Moy et al., where it is immaterial whether the avidin or streptavidin is used to bind to a biotin, one of ordinary skill in the art at the time of the invention would have found it obvious to substitute streptavidin for the avidin of Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito.

9. Claim 13 is rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al. (WO 97/46256, Dec. 11, 1997) in view of Rhode et al. (U.S. Patent No. 6,232,445, May 15, 2001), Lehmann et al. (U.S. Patent No. 5,939,281, Aug. 17, 1999), Yurino et al. (U.S. Patent No. 6,127,125, Oct. 3, 2000), and Alfenito (U.S. Patent No. 6,355,419 B1, Mar. 12, 2002) as applied to claims 1, 11, and 12 above, and further in view of Abraham

et al. (*J. Immunol.*, 20014, Vol. 167, pp5193-5201) and Mikesell et al. (U.S. PG Pub. No. US 2002/0095024, Filed on June 6, 2001).

Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito teaches an array comprising a substrate and an array of MHC molecules complexed with antigen-derived peptides and costimulatory antibodies immobilized in spatially distinct areas on the substrate as set forth above. Webb et al. further teaches the costimulatory molecules include ICAM's (ICAM-1, ICAM-2, and ICAM-3, p72, line 14-p74, line 20). Activation of T cells is characterized by proliferation of the responsive T cell population coordinated with the selection of cytokines (p16, lines 28-32). However, Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito fails to teach an array, wherein the costimulatory antibodies bind specifically to CD11a.

Abraham et al. teaches that integrin LFA-1 serves as an accessory molecule in T cell activation (see entire document). The primary pathway whereby engagement of LFA-1 through its ligand ICAM-1 up-regulates IL-2 gene expression through enhanced IL-2 transcription (Abstract). Further, a number of anti-LFA-1 Abs has agonist/costimulatory activity such as anti-CD11a mAb (p5197, right column).

Mikesell et al. teaches that a first signal mediated by foreign antigens presented by MHC complexes causes T-cell entry into the cell cycle and a second signal, termed costimulation, causes cytokine production and T-cell proliferation (p1, paragraph [0003]).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to include anti-CD11a antibody of Abraham et al. as a

costimulatory antibodies in the array of Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito in order to provide costimulatory signal in addition to the antigenic signal of the MHC molecules complexed with antigen-derived peptides necessary for production of cytokines and T-cell proliferation, which can be used to detect T-cell activation/responsiveness. The advantage of delivering necessary costimulatory signal for T-cell characterization provides the motivation to combine teachings of Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito and Abraham et al. with a reasonable expectation of success as Mikesell et al. teaches that a first signal mediated by foreign antigens presented by MHC complexes causes T-cell entry into the cell cycle and a second signal, termed costimulation, causes cytokine production and T-cell proliferation.

Further, Webb et al. et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito meets the limitations of claim 13 except that it employs an ICAM's rather than anti-CD11a antibodies as costimulatory molecules. However, because these two elements were art-recognized equivalents at the time of the invention in the T-cell immunology arts, where it is immaterial whether the ICAM's or anti-CD11a antibodies are used to provide costimulatory signal to T-cells, one of ordinary skill in the art at the time of the invention would have found it obvious to substitute anti-CD11a antibodies for the ICAM's of Webb et al. in view of Rhode et al., Lehmann et al., Yurino et al., and Alfenito.

Response to Arguments

10. Prematurity of Finality of Office Action

Applicant's argument in the reply filed on November 12, 2009 regarding the prematurity of the Final Office Action dated May 12, 2009 has been fully considered but is not found persuasive essentially for the reasons of record. As stated in the Final Office Action dated May 12, 2009, the new grounds of rejections have been necessitated by the amendments to claims 1, 3, and 4 dated April 28, 2008. Specifically, Webb fails to teach that at least one hydrophobic barrier surrounds a plurality of the spatially-distinct areas and each of the spatially-distinct areas is not surrounded individually by a separate hydrophobic barrier, such that when a single volume of sample is applied inside of the at least one hydrophobic barrier, all areas in the plurality of said spatially-distinct areas are in contact with the single volume of sample. The limitation of "hydrophobic barrier surrounds a plurality of the spatially-distinct areas and each of the spatially-distinct areas is not surrounded individually by a separate hydrophobic barrier" was previously not presented. See MPEP § 706.07 [R-3].

In view of the foregoing response to arguments, the finality of the Final Office Action dated May 12, 2009 is considered proper and maintained.

11. Rejection of claims 1-7, 11, 12, 16, 20, and 25 under 35 U.S.C. 103(a) as being unpatentable over Webb in view of Rhode, Lehmann, Yurino, and Alfenito

Applicant's arguments filed on November 11, 2009 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed herein.

In response to applicant's argument that Yurino and Alfenito is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). Although both Yurino and Alfenito includes embodiments related to nucleic acid arrays, Yurino (column 3, lines 3-18) and Alfenito (column 7, lines 26-47) further includes other embodiments related to protein arrays. Webb teaches arrays related to immobilizing proteins on the array surface for cell-based assays as set forth above. Similarly, Rhode and Lehmann teach activating T cells using protein receptor molecules. Since teachings of Webb, Rhode, Lehmann, Yurino, and Alfenito involve investigating specific protein interactions, one of ordinary skill in the art would recognize that Yurino and Alfenito are reasonably pertinent to the biochip/array formats appropriate for immobilization of biomolecules such as proteins as recited in the claims.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, Webb fails to teach that at least one hydrophobic barrier surrounds a plurality of the spatially-distinct

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areas and each of the spatially-distinct areas is not surrounded individually by a separate hydrophobic barrier, such that when a single volume of sample is applied inside of the at least one hydrophobic barrier, all areas in the plurality of said spatially-distinct areas are in contact with the single volume of sample. However, Yurino teaches a biochip comprising a plurality of regions bound with various probes as set forth above (see entire document, particularly Abstract). The biochip has a flat upper surface of a generally equal height. As a result, a sample can be applied to the entire features of the biochip (column 6, lines 48-60). Alfenito teaches an array of probes comprising a nylon membrane; a plurality of subarrays of probes on the nylon membrane, the subarrays comprising a plurality of individual spots wherein each spot is comprised of a plurality of probes of the same sequence; and a plurality of hydrophobic barriers located between the subarrays on the nylon membrane, whereby the plurality of hydrophobic barriers prevents cross contamination between adjacent subarrays (see entire document, particularly column 3, lines 5-14) as set forth above. Many samples may be interrogated as pools at the same subarrays or independently with different subarrays within one support (column 35, lines 55-63). Given the teachings of Yurino, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to employ the flat surface for the protein microarrays of Webb as taught by Yurino in order to apply a sample to all the features of the protein microarray. The ease of applying sample to desired regions of the protein microarray provides the motivation to combine teachings of Webb and Yurino with a reasonable expectation of success. In addition, because both flat and non-flat substrates be used to provide support for the

protein arrays, it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute the multi-well plate format of Webb for the flat substrate format of Yurino to achieve to predictable result of providing a suitable support for the protein array. Further, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to provide at least one hydrophobic barrier surrounding a plurality of the spatially-distinct areas (each of the spatially-distinct areas is not surrounded individually by a separate hydrophobic barrier) such that when a single volume of sample is applied inside of the at least one hydrophobic barrier, all areas in the plurality of said spatially-distinct areas are in contact with the single volume of sample as taught by Alfenito in the array of Webb in order to prevent cross contamination between adjacent subarrays for simultaneous analysis of multiple samples. The advantage of analyzing multiple samples simultaneously with cross contamination provides the motivation to combine teachings of Webb and Alfenito with a reasonable expectation of success.

The Declaration of Lawrence J. Stern, Ph.D. under 37 CFR 1.132 filed on November 12, 2009 is insufficient to overcome the rejection of claims 1-9, 11-13, 16, 20, and 25 based upon rejections under 35 U.S.C. 103(a) as set forth in the last Office action. The declaration asserts that there would have been no reasonable expectation of success in making the combination of Webb, Rhode, Lehmann, Yurino, and Alfenito given the time course of experiments and the size of the molecules. The declaration further asserts that in the case of the methods for which the presently claimed arrays are configured, the assay takes place over a period of many hours to days; the living

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cells in the assay would be expected to diffuse through the media and, once activated, secrete the cytokines into the general solution. Given the long time frame of the assay, one of skill in the art would expect that the diffusion of the T cells and secreted cytokines into the solution would result in such an immense amount of background staining that the individual areas would be indistinguishable, and that the arrays would be useless for identifying from which cell the cytokines are secreted. According to the Declaration, T cell mobility arrest can occur, but this process requires a constellation of adhesion molecules on the antigen presenting cells and lateral mobility of MHC molecules on the APC surface. However, Webb teaches that adhesion molecules such as ICAMs and LFAs mediate cell adhesion (p22, lines 14-30). Webb further teaches the T cell activation can be achieved by MHC presentation of foreign peptides in combination with costimulatory signals via costimulatory molecule such as CD80 and CD86 (p21, line 5-p22, line 11). The combination of T cell activation via MHC, costimulatory molecules, and adhesion molecules, one of ordinary skill in the art would have had a reasonable expectation of success in providing T cell adhesion to the array surface. In contrast to applicant's arguments, T cell mobility arrest can occur and individual areas capturing cytokines secreted by the neighboring T cells would not be indistinguishable.

The Declaration of Lawrence J. Stern further asserts that there would have been no reasonable expectation of success in making the combination of Webb, Rhode, Lehmann, Yurino, and Alfenito given diffusion characteristics of cytokines and the sizes and spacings of spatially distinct areas. However, Assenmacher et al. (U.S. Patent No.

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6,576,428 B1, filed May 10, 1999) teaches a method of cytokine capture assay, in which cytokine being secreted by activated T cells in a solution is being captured by the capture moiety present on the surface of the activated T cells (see entire document, particularly column 7, line 56-column 8, line 6). Assenmacher et al. therefore shows that cytokines are immediately captured by the capture molecules present in the vicinity of the secreting T cells. In addition, Christel et al. (U.S. Patent No. 6,368,871 B1, Apr. 9, 2002) teaches that mixing by diffusion in microfluidic environment can be very slow (see entire document, particularly column 4, lines 10-28). Therefore, one of ordinary skill in the art would have had a reasonable expectation of success in capturing cytokines being secreted by the T cells present on the array surface before significant diffusion effects.

In view of the foregoing response to arguments, the rejection of claims 1-7, 11, 12, 16, 20, and 25 under 35 U.S.C. 103(a) as being unpatentable over Webb in view of Rhode, Lehmann, Yurino, and Alfenito has been maintained.

12. Rejection of claims 8 and 9 under 35 U.S.C. 103(a) as being unpatentable over Webb in view of Rhode, Lehmann, Yurino, and Alfenito, and further in view of Tom-Moy

Applicant's arguments filed on November 11, 2009 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed above.

In view of the foregoing response to arguments, the rejection of claims 8 and 9 under 35 U.S.C. 103(a) as being unpatentable over Webb in view of Rhode, Lehmann, Yurino, and Alfenito, and further in view of Tom-Moy has been maintained.

13. Rejection of claim 13 under 35 U.S.C. 103(a) as being unpatentable over Webb in view of Rhode, Lehmann, Yurino, and Alfenito, and further in view of Abraham and Mikesell

Applicant's arguments filed on November 11, 2009 have been fully considered but they are not persuasive essentially for the reasons of record and arguments addressed above.

In view of the foregoing response to arguments, the rejection of claim 13 under 35 U.S.C. 103(a) as being unpatentable over Webb in view of Rhode, Lehmann, Yurino, and Alfenito, and further in view of Abraham and Mikesell has been maintained.

Since the prior art fulfills all the limitations currently recited in the claims, the invention as currently recited would read upon the prior art.

Conclusion

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to UNSU JUNG whose telephone number is (571)272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Unsu Jung/
Unsu Jung
Primary Examiner
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